

TECHNICAL ABSTRACT

A Phase I Study of the Safety of Inducible Nitric Oxide Synthase Gene Therapy for the Prevention of Intimal Hyperplasia in Arteriovenous Grafts used for Hemodialysis Access

The creation and maintenance of vascular access for hemodialysis is a great financial burden in the United States and the source for tremendous morbidity and mortality among end-stage renal failure patients. The most commonly placed access is the arteriovenous (AV) graft which utilizes a polytetrafluoroethylene (PTFE) graft placed in the forearm or upper arm, serving as a conduit between an artery and a vein. It accounts for ~70% of all permanent hemodialysis accesses. These grafts, unfortunately, are subject to intimal hyperplasia at the venous anastomoses that results in AV graft dysfunction and ultimately thrombosis. Approximately 30% of patients with AV grafts experience hemodynamically significant neointima formation by 6 months after graft placement. Even at the best vascular surgery centers, the 3 year cumulative patency for AV grafts is only ~50%. Over \$1 billion is spent in the United States annually on hospital costs related to hemodialysis access procedures and the total cost of hemodialysis complications is about twice that value.

Nitric oxide (NO) mediates vascular smooth muscle cell (SMC) relaxation, inhibits platelet and leukocyte adhesion, and prevents SMC proliferation (1). The vasculature is normally bathed in NO derived from the endothelium. At sites of vascular injury, the endothelium is disrupted and injured and local NO production is reduced or completely abolished. The loss of local NO availability has been shown to be the basis for vascular smooth muscle cell proliferation and intimal hyperplasia at the site of injury and the subsequent development of local stenosis or occlusion. The role of NO in intimal hyperplasia has been substantiated because replacing or augmenting NO availability at sites of vascular injury prevents intimal hyperplasia. We propose that local NO delivery through the use of adenoviral gene therapy techniques will locally augment NO production. The ideal gene for this application is the inducible NO synthase (iNOS) isoform which produces high levels of NO. The greater enzymatic activity of iNOS as compared with the other isoforms may yield greater clinical efficacy with lower gene transfer efficiency and the use of lower concentrations of viral vector. We have already established that adenovirus mediated iNOS gene delivery to several different animal models of vascular injury dramatically reduced intimal hyperplasia (2,3).

We propose that iNOS gene transfer using an adenoviral vector (AdiNOS) may be effective at inhibiting intimal hyperplasia in AV grafts and thereby prolonging the patency of the grafts and reducing the associated morbidity of graft thrombosis. We will perform a dose escalation study to determine the highest and safest dose of adenoviral vector to use for subsequent efficacy studies. The AdiNOS will be applied directly to the lumen of the vein to be anastomosed to the graft at the time of surgical placement of the graft and the vector will be evacuated so that systemic administration is avoided. Approximately 10-30 patients will be enrolled at a single center and the viral titers that will be tested are 1×10^9 , 1×10^{10} , and 1×10^{11} viral particles. The highest dose of AdiNOS was not associated with any significant toxicity in preclinical studies in rats or pigs.

References:

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